REMARKS

In view of the remarks put forth below, reconsideration and allowance are of the pending claims is respectfully requested.

FORMAL MATTERS:

Claims 1, 3, 6, 9, 10, and 15 have been amended. Support for these amendments is found in the Specification and claims as filed. Accordingly, no new matter is added.

Claims 5, 7, 12-14, and 16-18 have been cancelled without prejudice.

Claims 1-4, 6, 8-11, and 15 are pending and under examination after entry of the amendments above.

REJECTION UNDER 35 U.S.C. §102

The Examiner rejected Claims 1-3 and 7-10 under 35 U.S.C. §102(e) as allegedly being anticipated by Stiefel et al. (U.S. Patent No. 6,656,509).

The Office Action had indicated that the Examiner rejected Claims 1-3, 7-10, 9 under 35 U.S.C. §102(e) as allegedly being anticipated by Stiefel et al. (U.S. Patent No. 6,656,509). In a telephone conversation with the Examiner on March 19, 2009, the Examiner clarified that the rejection is of Claims 1-3 and 7-10 under 35 U.S.C. §102(e).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, (Fed. Cir. 1987).

Claim 1 has been amended to recite "administering to a subject having a tumor a pharmaceutically acceptable salt of an inorganic selenium-containing compound (iSe compound) in an amount effective to alter a reduction-oxidation state of a tumor cell toward oxidation; and administering radiation therapy to the subject." (emphasis added)

Claim 10 has been amended to recite "administering to a subject having a tumor a pharmaceutically acceptable salt of an inorganic selenium-containing (iSe) compound in an amount effective to sensitize the tumor to radiation therapy; and administering the radiation therapy to the subject." (emphasis added)

As amended, an element of the rejected claims is radiation therapy. Paragraph [0036] of the present specification, shown below, discusses the ability of the combination of an inorganic selenium compound and radiotherapy to kill cancerous cells.

> The invention for the first time demonstrates that an inorganic selenium containing compound (referred to herein as "iSe compound"), such as inorganic selenite, renders tumors more sensitive to other cancer therapies, such as radiotherapy, especially when administered prior to administration of the second cancer therapy, e.g., so as to allow for iSe metabolism and alteration of the tumor cell redox state with accompanying generation of ROS. Furthermore, the invention also provides a method that provides for a strong preference for killing cancerous cells. The invention finds particular use where the iSe compound is administered in conjunction with, and particular prior to, administration of a cancer therapy that creates or provides reactive oxygen species (ROS) in a cancerous cell. (emphasis added)

Thus, the combination of an inorganic selenium compound and radiotherapy is cytotoxic, as the combination can kill cancerous cells.

On the other hand, Stiefel fails to disclose radiation therapy. At column 4, Stiefel discloses the following:

> It is therefore the object of the present invention to provide a possibility of enhancing the effect of antitumor drugs and to provide said drugs in a suitable form of administration.
> This object is achieved by using selenium and/or at least one selenium compound for enhancing the effect of a cytostatic or a mixture of cytostatics. (emphasis added)

As described in Stiefel, a "cytostatic" agent is an agent that inhibits mitosis or inhibits nucleic acid synthesis. See column 6, lines 7-16 and column 9, lines 15-22 of Stiefel. Thus, Stiefel discloses cytostatic agents, not cytotoxic cancer therapy. Indeed, Stiefel does not disclose radiation therapy. As such, Stiefel fails to disclose all the elements of the rejected claims.

Therefore, the Applicants contend that Stiefel et al. does not anticipate the rejected claims. In view of the above, the Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §102(e).

REJECTION UNDER 35 U.S.C. §103(A)

The Examiner rejected Claims 1-18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Stiefel et al. (U.S. Patent No. 6,656,509) in view of Lemelson (U.S. Patent No.

4,665,897) and Gorun (U.S. Patent No. 6,511,971). This rejection is respectfully traversed as applied and as it may be applied to the amended claims.

In making this rejection, the Examiner states the following:

> The difference between Stiefel et al. and the claimed invention is that Stiefel et al. does not disclose the use of inorganic selenite, radiation therapy or reactive oxygen species (ROS)-inducing therapy. However, the prior art amply suggest the same as Stiefel discloses that sodium selenite is a preferred source of selenium, the application acknowledges that radiotherapy is used to treat prostate cancer, Lemelson discloses use of radiation therapy using neutron beams to active nuclide species at the site of the tumor and Gorun discloses that photodynamic sensitizers which produce singlet molecular oxygen are used to destroy cancerous tissue. As such, one of ordinary skill in the art would have expected that the combination of sodium selenite with other methods of treatment of cancers and tumors would be effective in treating cancers and tumors such as prostate cancer.

The Applicants submit that the combination of the references does not render the claimed invention obvious because the combination of the cited references fails to provide one of skill in the art with predicted success in the claimed methods.

In addition to demonstrating that all elements were known in the prior art, the Office must provide evidence that the combination would be "a predicted success." This principle is illustrated in *three* Supreme Court cases[1] decided prior to *KSR*, and is a recurring theme of *KSR*. For example, in *KSR*, the Supreme Court stated that in order for a combination of elements to be patentable, "the combination must do more than yield a predictable result".[2] Likewise, the corollary principle, namely that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results"[3] is also discussed. The Supreme Court in *KSR* also stated that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions".[4]

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[1] *United States* v. *Adams*, 383 U.S. 39, 40 (1966); *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, 396 U.C. 57, 60-62 (1969); and *Sakraida* v. *AG Pro, Inc.*, 425 U.C. 273, 282 (1976).
[2] *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007).
[3] *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007).
[4] *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007); emphasis added.

Thus, according to the Supreme Court, an analysis of the "predictable success" of a combination of known elements may be used to separate patentable combinations (e.g., a battery that contains water, in the case of *United States* v. *Adams*, *supra*) from those that are unpatentable (e.g., an adjustable pedal having a fixed pivot point and a sensor, in the case of *KSR, supra*).

MPEP §2145 sets out the principles in considering rebuttal arguments by applicants against obviousness, stating in part that: "Rebuttal evidence may also include evidence that the claimed invention yields *unexpectedly improved properties or properties not present in the prior art*. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties" (emphasis added).

The results of the claimed methods are unexpected and surprising based on knowledge and the state of the prior art.

Stiefel discloses the use of "selenium and/or at least one selenium compound for enhancing the effect of one or more cytostatics." As stated above, Stiefel fails to disclose radiation therapy.

Lemelson discloses "methods for detecting and treating abnormal tissue growth, such as benign and malignant tumors in living beings including, but not limited to the use of drug units formed of monoclonal antibodies containing or combined with units or small quantities of elements or compounds which either generate low levels of radiation per se or which may be activated to generate radiation for either detection purposes or a combination of detection and treatment purposes."

Goron discloses "a method for treating a condition in a patient, by administering to the patient an effective amount of a [certain] phthalocyanine compound. In one embodiment, the method comprises exposing the patient to light to achieve photodynamic therapy."

The presently claimed methods are based on discovery that there is a synergistic effect with a combination of a pharmaceutically acceptable salt of an inorganic selenium-containing compound and radiation therapy to treat neoplastic disease, to enhance sensitivity of a tumor, and to treat prostate cancer. One of ordinary skill in the art would not reasonably expect that a combination of a pharmaceutically acceptable salt of an inorganic selenium-containing compound and radiation therapy would produce synergistic results.

Examples 5 and 6 show examples of the synergistic effect of the combination of an inorganic selenium-containing compound and radiation therapy. Example 5 uses LAPC-4 cells and Example 6 uses DU 145 cells, both of which are prostate cancer cells. The results are measured by survival fraction, which is calculated as the plating efficiency of treated cells divided by the plating efficiency of untreated cells. SF_2 is the survival fraction of exponentially growing cells that were irradiated at the clinically relevant dose of 2 Gy. See Paragraph [0115] of Specification.

Example 5 states, *inter alia*:

In order to assess the effects of higher doses of γ-radiation, LAPC-4 cells were treated with 10 μM selenite for 6 hours prior to receiving 2 Gy or 5 Gy γ-irradiation. Survival was measured using a clonogenic assay. This treatment regimen was based upon the data above showing that treatment of LAPC-4 cells with 10 μM selenite for 6 hours decreased the GSH:GSSG ratio 88.3%. The surviving fraction of LAPC-4 cells after treatment with selenite alone was 0.431+-0.021 (data not shown). In experiments, in which selenite was combined with radiation, the results were normalized for the killing from selenite alone. Selenite enhanced radiation-induced inhibition of colony formation (SF_2=0.056) compared to cells treated with radiation alone (SF_2=0.244) (FIG. 12). These results indicate that selenite inhibits the clonal growth of LAPC-4 cells and enhances the effect of radiation on these cells.

Example 6 states, *inter alia*:

The effects of selenite on the response of DU 145 cells to γ-irradiation were studied using clonogenic survival assays. The surviving fractions of DU 145 cells treated with 10 μM selenite for 6 or 12 hours alone (and assessed at 17 days after irradiation) were 0.941 and 0.409, respectively (data not shown). After normalization for the killing from selenite alone, pre-treatment with selenite enhanced radiation-induced cell death (SF_2=0.343 and 0.199 at 6 and 12 hours, respectively) compared to cells treated with radiation alone (SF_2=0.554) (FIG. 13, Panel B).

The survival fractions and SF_2 from Examples 5 and 6 are summarized in the table below.

Cell line	Treatment	Survival Fraction or SF_2
LAPC-4	Selenite alone	0.431
	Radiation alone	0.244
	10 μM Selenite and 6 hr pre radiation	**0.056**

DU 145	10 μM Selenite alone 6hr	0.941
	10 μM Selenite alone 12 hr	0.409
	Radiation alone	0.554
	10 μM Selenite and 6 hr pre radiation	**0.343**
	10 μM Selenite and 12 hr pre radiation	**0.199**

Also, Example 10 shows an example of effect of selenite and radiation as combination therapy with *in vivo* results in an animal model. Example 10 states:

> Mice with well-established LAPC-4 tumors were treated with selenite alone, local tumor radiation alone, or selenite with localized tumor radiation. [S]elenite significantly enhanced local radiation-induced tumor growth delay. The effect of the combined treatment was significantly greater than that of radiation or selenite alone. Furthermore, selenite treatment was very well tolerated, and there was no significant weight loss in the selenite treated mice compared to the group of mice treated with local tumor irradiation alone.

Thus, as concluded from Examples 5 and 6, the results indicate that selenite enhances the effect of radiation on LAPC-4 and DU 145 cells. The survival fractions of the combination of selenite and radiation are significantly lower than the survival fraction of selenite alone and radiation alone. Further, as supported by the study set out in Example 10, a combination of selenite and radiation has a significantly greater effect than selenite alone and radiation alone as shown in the *in vivo* animal models.

MPEP §716.02(e) states that "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ...of the claims at issue." The cited reference Stiefel discloses a selenium compound, but not radiation therapy, as recited in the present claims. The cited reference Lemelson discloses radiation therapy, but not a pharmaceutically acceptable salt of an inorganic selenium-containing compound. The cited reference Gorun discloses a photosensitizing compound, but not a pharmaceutically acceptable salt of an inorganic selenium-containing compound. Applicants submit that one of ordinary skill in the art, even in view of Siefel, Lemelson, and Gorun would not reasonably expect that a combination of a pharmaceutically acceptable salt of an inorganic selenium-containing compound and radiation therapy would synergistically inhibit the growth of cancer cells with predictable success under

the *KSR* standard. Indeed, the results from Examples 5, 6, and 10 show synergistic effect for a combination of a pharmaceutically acceptable salt of an inorganic selenium-containing compound and radiation therapy that would not have been predicted by one of ordinary skill in the art.

In light of the above arguments, it is submitted that the cited combination of references fails to provide the requisite predicted success in the claimed methods. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §103(a).

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-333.

Respectfully submitted,
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